

IN THE CLAIMS

Please amend claims 116, 164, and 226 as shown below. The following listing of claims replaces all prior listings.

1-115. (Canceled).

116. (Currently amended) A method for the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, comprising:

(i) administering said bioactive agent to said patient;

(ii) administering a vesicle composition to said patient, by intravascular infusion, wherein said vesicle composition comprises, in an aqueous carrier, vesicles comprising lipids, proteins, or polymers and a gas or gaseous precursor; and

(iii) ~~delivering said bioactive agent into said selected tissue by~~ cavitating and/or rupturing said vesicles, thereby delivering said bioactive agent from the vasculature to a selected tissue in a patient,

wherein said cavitating and/or rupturing is accomplished by applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz in the amount sufficient to produce said cavitating and/or rupturing, with the further proviso that between about 1 and 10 mol. per cent of said lipids comprise negatively charged lipids.

117. (Previously presented) A method according to Claim 116 wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

118. (Previously presented) A method according to Claim 116 wherein said bioactive agent and said vesicle composition are administered to said patient substantially simultaneously.

119. (Previously presented) A method according to Claim 116 further comprising imaging said patient using diagnostic ultrasound imaging.
120. (Previously presented) A method according to Claim 116 wherein said vesicles comprise lipids.
121. (Previously presented) A method according to Claim 120 wherein said vesicle composition comprises vesicles selected from the group consisting of micelles and liposomes.
122. (Previously presented) A method according to Claim 120 wherein said lipids comprise phospholipids.
123. (Previously presented) A method according to Claim 122 wherein said phospholipids are selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid.
124. (Previously presented) A method according to Claim 123 wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.
125. (Previously presented) A method according to Claim 124 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.
126. (Previously presented) A method according to Claim 123 wherein said phosphatidylethanolamine is selected from the group consisting of dipalmitoylphosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

127. (Previously presented) A method according to Claim 126 wherein said phosphatidylethanol-amine comprises dipalmitoylphosphatidylethanolamine.

128. (Previously presented) A method according to Claim 123 wherein said phosphatidic acid comprises dipalmitoylphosphatidic acid.

129. (Previously presented) A method according to Claim 120 wherein said lipid further comprises a polymer.

130. (Previously presented) A method according to Claim 129 wherein said polymer comprises a hydrophilic polymer.

131. (Previously presented) A method according to Claim 130 wherein said hydrophilic polymer comprises polyethylene glycol.

132-137. (Canceled).

138. (Previously presented) A method according to Claim 116 wherein said gas comprises a fluorinated gas.

139. (Previously presented) A method according to Claim 138 wherein said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride.

140. (Previously presented) A method according to Claim 139 wherein said fluorinated gas comprises a perfluorocarbon.

141. (Previously presented) A method according to Claim 140 wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

142-145. (Canceled).

146. (Previously presented) A method according to Claim 116 wherein said vesicle composition is administered to the patient at a rate of from about 1×10^6 to less than about 8×10^6 vesicles/Kg-sec.

147. (Previously presented) A method according to Claim 146 wherein said vesicle composition is administered at a rate of from about 1×10^6 to about 7×10^6 vesicles/Kg-sec.

148. (Previously presented) A method according to Claim 147 wherein said vesicle composition is administered at a rate of from about 1.5×10^6 to about 6×10^6 vesicles/Kg-sec.

149. (Previously presented) A method according to Claim 148 wherein said vesicle composition is administered at a rate of from about 2×10^6 to about 5.5×10^6 vesicles/Kg-sec.

150. (Previously presented) A method according to Claim 149 wherein said vesicle composition is administered at a rate of from about 2.5×10^6 to about 5×10^6 vesicles/Kg-sec.

151. (Previously presented) A method according to Claim 150 wherein said vesicle composition is administered at a rate of from about 3×10^6 to about 4.5×10^6 vesicles/Kg-sec.

152-159.(Canceled).

160. (Previously presented) A method according to Claim 116 wherein said bioactive agent is selected from the group consisting of a diagnostic agent, genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic

agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, a thrombolytic agent, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

161-163. (Canceled).

164. (Currently amended) A method the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to said patient;

(ii) administering an acoustically active composition to said patient, by intravascular infusion; and

iii) ~~delivering said bioactive agent into said selected tissue by~~ activating said acoustically active composition, thereby delivering said bioactive agent from the vasculature to a selected tissue in a patient,

wherein said activating is accomplished by applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz in the amount sufficient to produce said activating.

165. (Previously presented) A method according to Claim 164 wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

166. (Previously presented) A method according to Claim 164 wherein said bioactive agent and said acoustically active composition are administered to said patient substantially simultaneously.

167. (Canceled).

168. (Previously presented) A method according to Claim 164 wherein said tissue comprises an area of reduced blood perfusion.

169. (Previously presented) A method according to Claim 168 wherein said area of reduced blood perfusion comprises ischemic tissue.

170. (Previously presented) A method according to Claim 164 wherein said tissue comprises myocardium.

171. (Previously presented) A method according to Claim 164 wherein said tissue comprises glandular tissue.

172. (Previously presented) A method according to Claim 171 wherein said glandular tissue comprises the prostate gland.

173. (Previously presented) A method according to Claim 164 further comprising imaging said tissue using diagnostic ultrasound imaging.

174. (Previously presented) A method according to Claim 164 wherein said bioactive agent comprises an agent selected from the group consisting of a diagnostic agent, genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, a thrombolytic agent, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

175-177. (Canceled).

178. (Previously presented) A method according to Claim 174 wherein said acoustically active composition and bioactive agent are administered prior to said application of ultrasound energy.

179. (Previously presented) A method according to Claim 174 wherein said acoustically active composition and bioactive agent are administered at about the same time as said application of ultrasound energy.

180. (Withdrawn) A method according to Claim 174 further comprising applying radiation energy to said tissue.

181. (Withdrawn) A method according to Claim 179 wherein said acoustically active composition and bioactive agent are administered prior to said application of radiation energy.

182. (Withdrawn) A method according to Claim 180 wherein said acoustically active composition and bioactive agent are administered at about the same time as said application of radiation energy.

183. (Withdrawn) A method according to Claim 178 wherein said acoustically active composition and bioactive agent are administered from about 1 minute to about 8 hours prior to said application of ultrasound energy.

184. (Withdrawn) A method according to Claim 181 wherein said acoustically active composition and bioactive agent are administered from about 1 minute to about 8 hours prior to said application of radiation energy.

185. (Withdrawn) A method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, comprising:

(i) administering said bioactive agent to said patient;

(ii) administering a vesicle composition to said patient, by intravascular infusion, wherein said vesicle composition comprises, in an aqueous carrier, vesicles comprising lipids, proteins, or polymers and a gas or gaseous precursor; and

(iii) cavitating and/or rupturing said vesicles by applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz, to thereby enhance delivery of said bioactive agent from the vasculature through the vessel wall and into said selected tissue,

wherein said bioactive agent is selected from the group consisting of a genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

186. (Withdrawn) A method according to Claim 185, wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

187. (Withdrawn) A method according to Claim 185, wherein said bioactive agent and said vesicle composition are administered to said patient substantially simultaneously.

188. (Withdrawn) A method according to Claim 185, wherein said vesicles comprise lipids.

189. (Withdrawn) A method according to Claim 188, wherein said vesicle composition comprises vesicles selected from the group consisting of micelles and liposomes.

190. (Withdrawn) A method according to Claim 188, wherein said lipids comprise phospholipids.

191. (Withdrawn) A method according to Claim 190, wherein said phospholipids are selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid.

192. (Withdrawn) A method according to Claim 191, wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

193. (Withdrawn) A method according to Claim 192, wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

194. (Withdrawn) A method according to Claim 191, wherein said phosphatidylethanolamine is selected from the group consisting of dipalmitoylphosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

195. (Withdrawn) A method according to Claim 194, wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

196. (Withdrawn) A method according to Claim 191, wherein said phosphatidic acid comprises dipalmitoylphosphatidic acid.

197. (Withdrawn) A method according to Claim 188, wherein said lipid further comprises a polymer.

198. (Withdrawn) A method according to Claim 197, wherein said polymer comprises a hydrophilic polymer.

199. (Withdrawn) A method according to Claim 198, wherein said hydrophilic polymer comprises polyethylene glycol.
200. (Withdrawn) A method according to Claim 185, wherein said gas comprises a fluorinated gas.
201. (Withdrawn) A method according to Claim 200, wherein said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride.
202. (Withdrawn) A method according to Claim 201, wherein said fluorinated gas comprises a perfluorocarbon.
203. (Withdrawn) A method according to Claim 202, wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.
204. (Withdrawn) A method according to Claim 185, wherein said vesicle composition is administered to the patient at a rate of from about 1×10^6 to less than about 8×10^6 vesicles/Kg-sec.
205. (Withdrawn) A method according to Claim 204, wherein said vesicle composition is administered at a rate of from about 1×10^6 to about 7×10^6 vesicles/Kg-sec.
206. (Withdrawn) A method according to Claim 205, wherein said vesicle composition is administered at a rate of from about 1.5×10^6 to about 6×10^6 vesicles/Kg-sec.
207. (Withdrawn) A method according to Claim 206, wherein said vesicle composition is administered at a rate of from about 2×10^6 to about 5.5×10^6 vesicles/Kg-sec.

208. (Withdrawn) A method according to Claim 207, wherein said vesicle composition is administered at a rate of from about 2.5×10^6 to about 5×10^6 vesicles/Kg-sec.

209. (Withdrawn) A method according to Claim 208, wherein said vesicle composition is administered at a rate of from about 3×10^6 to about 4.5×10^6 vesicles/Kg-sec.

210. (Withdrawn) A method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to said patient;

(ii) administering an acoustically active composition to said patient, by intravascular infusion; and

(iii) activating said acoustically active composition by applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz, to thereby enhance delivery of said bioactive agent from the vasculature into said selected tissue,

wherein said bioactive agent is selected from the group consisting of a genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

211. (Withdrawn) A method according to Claim 210, wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

212. (Withdrawn) A method according to Claim 210, wherein said bioactive agent and said acoustically active composition are administered to said patient substantially simultaneously.

213. (Withdrawn) A method according to Claim 210, wherein said tissue comprises an area of reduced blood perfusion.

214. (Withdrawn) A method according to Claim 213, wherein said area of reduced blood perfusion comprises ischemic tissue.

215. (Withdrawn) A method according to Claim 210, wherein said tissue comprises myocardium.

216. (Withdrawn) A method according to Claim 210, wherein said tissue comprises glandular tissue.

217. (Withdrawn) A method according to Claim 216, wherein said glandular tissue comprises the prostate gland.

218. (Withdrawn) A method according to Claim 210, further comprising imaging said tissue using diagnostic ultrasound imaging.

219. (Withdrawn) A method according to Claim 210, wherein said acoustically active composition and bioactive agent are administered prior to said application of ultrasound energy.

220. (Withdrawn) A method according to Claim 210, wherein said acoustically active composition and bioactive agent are administered at about the same time as said application of ultrasound energy.

221. (Withdrawn) A method according to Claim 210, further comprising applying radiation energy to said tissue.
222. (Withdrawn) A method according to Claim 221, wherein said acoustically active composition and bioactive agent are administered prior to said application of radiation energy.
223. (Withdrawn) A method according to Claim 221, wherein said acoustically active composition and bioactive agent are administered at about the same time as said application of radiation energy.
224. (Withdrawn) A method according to Claim 219, wherein said acoustically active composition and bioactive agent are administered from about 1 minute to about 8 hours prior to said application of ultrasound energy.
225. (Withdrawn) A method according to Claim 223, wherein said acoustically active composition and bioactive agent are administered from about 1 minute to about 8 hours prior to said application of radiation energy.
226. (Currently amended) A method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, comprising:
- (i) administering said bioactive agent to said patient;
 - (ii) administering a vesicle composition to said patient, by intravascular infusion, wherein said vesicle composition comprises, in an aqueous carrier, the vesicles comprising lipids selected from the group consisting of micelles, liposomes, and phospholipids; and
 - (iii) cavitating and/or rupturing said vesicles by applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz in the amount sufficient to

produce said cavitating and/or rupturing, to thereby enhance delivery of said bioactive agent ~~from the vasculature through the vessel wall and~~ into said selected tissue,

wherein the phospholipids are selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid,

wherein:

(a) said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidyl-choline, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine;

(b) said phosphatidylethanolamine is selected from the group consisting of dipalmitoylphosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine; and

(c) said phosphatidic acid comprises dipalmitoylphosphatidic acid,

with the further proviso that between about 1 and 10 mol. per cent of said lipids comprise negatively charged lipids.

227. (Previously presented) A method according to Claim 226, wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

228. (Previously presented) A method according to Claim 226, wherein said bioactive agent and said vesicle composition are administered to said patient substantially simultaneously.

229. (Previously presented) A method according to Claim 226, further comprising imaging said patient using diagnostic ultrasound imaging.

230. (Previously presented) A method according to Claim 226, wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

231. (Previously presented) A method according to Claim 226, wherein said phosphatidylethanol-amine comprises dipalmitoylphosphatidylethanolamine.

232. (Previously presented) A method according to Claim 226, wherein said gas comprises a fluorinated gas.

233. (Previously presented) A method according to Claim 232, wherein said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride.

234. (Previously presented) A method according to Claim 233, wherein said fluorinated gas comprises a perfluorocarbon.

235. (Previously presented) A method according to Claim 234, wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

236. (Previously presented) A method according to Claim 226, wherein said vesicle composition is administered to the patient at a rate of from about 1×10^6 to less than about 8×10^6 vesicles/Kg-sec.

237. (Previously presented) A method according to Claim 236, wherein said vesicle composition is administered at a rate of from about 1×10^6 to about 7×10^6 vesicles/Kg-sec.

238. (Previously presented) A method according to Claim 237, wherein said vesicle composition is administered at a rate of from about 1.5×10^6 to about 6×10^6 vesicles/Kg-sec.

239. (Previously presented) A method according to Claim 238, wherein said vesicle composition is administered at a rate of from about 2×10^6 to about 5.5×10^6 vesicles/Kg-sec.

240. (Previously presented) A method according to Claim 239, wherein said vesicle composition is administered at a rate of from about 2.5×10^6 to about 5×10^6 vesicles/Kg-sec.

249. (Previously presented) A method according to Claim 240, wherein said vesicle composition is administered at a rate of from about 3×10^6 to about 4.5×10^6 vesicles/Kg-sec.

250. (Previously presented) A method according to Claim 226, wherein said bioactive agent is selected from the group consisting of a diagnostic agent, genetic material, a peptide, a beta-agonist, an anti-asthmatic, a steroid, a cholinergic agent, an anti-cholinergic agent, a 5-lipoxygenase inhibitor, a leukotriene inhibitor, an anti-neoplastic agent, an antibiotic, an anti-tumor drug, a radiation sensitizer, a thrombolytic agent, an anti-histamine, an anti-coagulant, an anti-inflammatory, a hormone, a growth factor, an angiogenic factor and a mitotic inhibitor.

251. (Previously presented) A method for the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, comprising:

(i) administering said bioactive agent to said patient;

(ii) administering a vesicle composition to said patient, by intravascular infusion, wherein said vesicle composition comprises, in an aqueous carrier, vesicles comprising phosphatidylethanolamine or phosphatidic acid, and a gas or gaseous precursor; and

(iii) delivering said bioactive agent into said selected tissue by cavitating and/or rupturing said vesicles,

wherein said cavitating and/or rupturing is accomplished by applying to the patient ultrasonic energy having a frequency between about 750 kHz and 3 MHz

252. (Previously presented) A method according to Claim 251, wherein said phosphatidylethanolamine is selected from the group consisting of dipalmitoylphosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

253. (Previously presented) A method according to Claim 251, wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

254. (Previously presented) A method according to Claim 251, wherein said phosphatidic acid comprises dipalmitoylphosphatidic acid.

255. (Previously presented) A method according to Claim 251, wherein said bioactive agent is administered to said patient at a rate which comprises continuous infusion.

256. (Previously presented) A method according to Claim 251, wherein said bioactive agent and said vesicle composition are administered to said patient substantially simultaneously.

257. (Previously presented) A method according to Claim 251, further comprising imaging said patient using diagnostic ultrasound imaging.

258. (Previously presented) A method according to Claim 251, wherein said gas comprises a fluorinated gas.

259. (Previously presented) A method according to Claim 258, wherein said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride.

260. (Previously presented) A method according to Claim 259, wherein said fluorinated gas comprises a perfluorocarbon.

261. (Previously presented) A method according to Claim 260, wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

262. (Previously presented) A method according to Claim 251, wherein said vesicle composition is administered to the patient at a rate of from about 1×10^6 to less than about 8×10^6 vesicles/Kg-sec.

263. (Previously presented) A method according to Claim 262, wherein said vesicle composition is administered at a rate of from about 1×10^6 to about 7×10^6 vesicles/Kg-sec.

264. (Previously presented) A method according to Claim 263, wherein said vesicle composition is administered at a rate of from about 1.5×10^6 to about 6×10^6 vesicles/Kg-sec.

265. (Previously presented) A method according to Claim 264, wherein said vesicle composition is administered at a rate of from about 2×10^6 to about 5.5×10^6 vesicles/Kg-sec.

266. (Previously presented) A method according to Claim 265, wherein said vesicle composition is administered at a rate of from about 2.5×10^6 to about 5×10^6 vesicles/Kg-sec.

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267. (Previously presented) A method according to Claim 266, wherein said vesicle composition is administered at a rate of from about 3×10^6 to about 4.5×10^6 vesicles/Kg-sec.